Syphilis in Pregnancy

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THE importance of syphilis in the mother during pregnancy has been emphasized repeatedly, particularly in regard to its effect upon the status of the child. This emphasis has been carried, in fact, almost to the point of a phobia as is shown by the widespread use of such terms as "disastrous outcome" or "syphilitic tragedy" when a child is stillborn or has syphilis, and "salvaged baby" when it is normal. It is reasonable to suppose that an investigator who uses such terms will be unlikely to view his data with critical and unbiased judgment and one is inclined to regard his conclusions with suspicion.

Most of the reports on the outcome of pregnancy in women with syphilis have come from obstetrical services and in nearly all there is lacking a clear explanation of the means by which a diagnosis of syphilis is established in the mother or the child. In mothers, the diagnosis usually depends on the serologic tests but reports rarely state whether the tests are strongly positive or whether they are regularly confirmed before treatment. In infants, the diagnosis is usually said to be based upon serologic tests, roentgenograms of the long bones, examination of the placenta and clinical observation of the child, but never is the exact role of these various factors specified. In most cases the diagnosis of syphilis seems to have been made as a result of positive serologic tests on the child at some specified time, usually one or two months, after birth, although it has been pointed out repeatedly that only by serial quantitative tests can the diagnosis be made with assurance, in the absence of clinical signs. We believe that many of the previous reports on this subject are unduly pessimistic in their attitude toward the effect of syphilis on the outcome of pregnancy, and the series of cases to be presented supports this belief.

This report is based upon the records of a group of patients from the Syphilis Clinic of the Stanford University School of Medicine. Three hundred and forty-one babies were born to 243 mothers during a period of a little over 15 years. One hundred and fifty-five of the mothers and 232 of the infants were white and the rest were negro. One hundred and eighty-five of the infants were male. Subdivision of the series according to race or sex of child revealed no significant differences and therefore the series is considered as a whole.

This clinical material differs in some respects from that presented by previous investigators. It was collected through the diagnosis file of the syphilis clinic and no patients who were not examined in that clinic are included. Deliveries that occurred prior to the registration of the mother in the syphilis clinic are not indexed and consequently almost no cases are included in which syphilis was not discovered until the time of delivery. The result is that we have very little completely untreated syphilis and a larger number of adequately treated cases, particularly among those treated before pregnancy, since many of our treated patients return to the clinic for subsequent prenatal care and delivery.

For patients who are receiving prenatal care, the obstetrical service sets up separate records which eventually get into the history but are not available during pregnancy. When abortion is threatened or when the child is known to have died in utero, the patient is frequently transferred to the San Francisco Hospital, and the Syphilis Clinic then has great difficulty in discovering the outcome, particularly with respect to whether or not the product of conception was examined and whether or not it showed evidence of syphilis. As a result, our figures on the incidence of abortion and stillbirth are quite incomplete and we have eliminated them entirely except for a few cases in which careful autopsies have been performed. In these circumstances, the child is classified as syphilitic if evidence of the disease is found, and as non-syphilitic if careful examination and spirochete stains show no evidence of the infection and there is sufficient reason for fetal death otherwise. Two such cases are included in the data on syphilitic infants and two among the non-syphilitic.

The role of syphilis in the production of abortion and stillbirth is somewhat uncertain. There is no doubt that the infection is responsible for a great many such terminations of pregnancy, but the custom of assigning all these accidents to syphilis when they occur in women who have the disease is to be deplored, since women who do not have syphilis also have abortions and stillbirths in appreciable numbers. In various reports on syphilis in pregnancy, the incidence varies widely. Thus Halloran [3] reports 12.5 per cent, McKelvey and Turner [7] 45.9 per cent, and McCord [6] 66.4 per cent of such terminations in mothers who have had no anti-syphilitic therapy. Both of the last two note a drop in this proportion to slightly over 10 per cent after extremely small amounts of treatment in the last few weeks of pregnancy. Such figures are distinctly misleading. Most syphilitic stillbirths occur from the sixth to the eighth month as a result of premature fetal death and it is much more probable that women who have entered the last month of pregnancy have somehow evaded the danger of fetal death, than that they have been saved from it by an insignificant amount of last-minute therapy.

We feel that the elimination of stillbirths from the data does not detract from the value of this study. A pregnancy that ends without a living child is an unpleasant experience for the mother that by no means approaches the distress that is caused by a

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living but chronically ill or defective child. We are primarily interested in the child that is born alive and we cannot subscribe to the use of such terms as "disastrous outcome" for those who do not survive the fetal period.

When an infant is born alive to a syphilitic mother, it may have some clinical evidence of syphilis at the time of birth or soon afterward, such as a skin eruption with positive darkfield, treponema pallidum in the umbilical cord or definite roentgenographic evidence of syphilis in the bones. In these circumstances, the diagnosis of congenital syphilis can usually be made promptly. When no clinical evidence of infection exists, the tests of blood from the cord may be positive or negative and in either case the diagnosis must be postponed, pending a period of further observation.

In recent years, roentenogram of the long bones, formerly considered an essential procedure in diagnosis, has fallen into some disrepute. In many infants with syphilis, the bones are normal, while in some normal infants confusing bone changes occur that make a diagnosis on this basis somewhat uncertain (Dill,[2] Ingraham,[4] Miller[8]). Examination of the placenta has also been shown to be of relatively little value in diagnosis.[2,8] Neither of these methods has been employed regularly in the present series. Many of the placentas were examined but rarely were any changes found that seemed to be of diagnostic significance.

The proof of syphilis in the infant depends, therefore, on clinical evidence of the disease at birth or during the first few weeks of life, or on tests on cord blood and on the blood of the infant, examined at intervals during its early life. These tests should be carried out by some quantitative procedure that permits a measure of the trend of the titer, and the diagnosis should never depend upon the persistence of a positive qualitative test for an arbitrarily selected period of time. The infants in this series were considered on this basis and the means by which the diagnoses were made will be explained. The children were examined, tested and treated by physicians in the Department of Pediatrics, and, although the follow-up was not always as thorough as it might have been, we believe it is possible to separate the syphilitic from the non-syphilitic infants with a considerable degree of certainty, as will be shown.

Two infants were stillborn and macerated and autopsy showed both to be infected heavily with treponema pallidum. These were the only cases in which an immediate clinical diagnosis of syphilis could be made. In three others darkfield positive lesions appeared in six weeks or less, with a rising serologic titer in the blood. In one of these there was a negative reaction in the cord blood, but the child's blood was weakly positive at five days and rapidly became strongly positive. In two more, a rising titer in the blood plus roentgenographic evidence of periostitis led to a diagnosis and in a third the roentgenographic evidence was supported by a moderately high but constant serologic titer.

In two cases the diagnosis was made on results of blood tests alone. One infant had a titer of 64 units at birth which remained constant for two months and went up to 256 in the third month. The other started with a titer of 10 units, which increased to 100 units at five weeks when treatment was started. No clinical evidence of syphilis developed in either of these children and they were not apparently injured by the delay in starting treatment. Altogether, there were ten infants in whom a definite diagnosis of congenital syphilis could be established.

In 107 infants, the cord blood was either strongly or partially positive, but the blood of the infant became negative without treatment. There were no recurrences. Sixty-five were followed for more than three months and 31 for over a year, and in no instance did any suspicious evidence of syphilis appear. Only seven were lost from observation in the first month, the others having been followed for a period of time that was sufficient to establish the diagnosis in most of the known syphilitics. There is no reason to suppose that any of these infants had syphilis.

There were 95 infants with negative cord blood reactions that were followed with repeated blood tests for various periods of time, 27 of them for more than a year. In none of them did any clinical or serologic evidence of syphilis appear. Another 99 apparently normal infants were born with negative cord blood reactions but had no further blood tests. Most of these infants had repeated physical examinations and quite adequate clinical follow-up, 75 for more than three months and 41 for more than a year. None developed anything to suggest syphilis and we consider them as uninfected since, with the one exception previously noted, we have never seen a child with a negative reaction in the cord blood develop congenital syphilis and most authorities concede that it is rare.

Another group consists of 30 infants originally diagnosed as having congenital syphilis (for which they were treated) on what appears to be completely inadequate evidence. They were treated prior to 1935 at a time when the urge to treat syphilis on the slightest provocation was exceptionally high. One was treated on the day of birth because of a skin eruption which was not darkfield positive. The results of blood tests were repeatedly negative and the child remained well except for chronic eczema through an observation period of nine years although the antisyphilitic therapy had been totally inadequate. In 11 cases the serologic tests were never stronger than doubtful. In 17 they were positive at birth but in no case was treatment delayed for more than five weeks for confirmation of the tests. In one case the cord blood reaction was positive, but tests of the infant's blood were doubtful at one month and almost negative at two, in spite of which treatment was administered. In no case was there ever any evidence of syphilis other than the serologic tests, in no case was a positive reaction obtained after treatment had been started, and no quantitative tests were performed.

According to Moore,[9] the minimum adequate treatment for early congenital syphilis should com-

prise 32 injections of mapharsen and 32 of bismuth over a period of one year. By this standard, all these patients were undertreated. Only one received adequate arsenical therapy and three adequate heavy metal. In the rest the total treatment was not over half of the required minimum and in only four was it continued for as long as a year.

Twenty-six of these 30 patients were followed for from one to 17 years with an average period of serologic observation of 5.2 years and of clinical observation of 7.3 years. Spinal fluid tests of most of them gave negative results. In none did any evidence of syphilis develop in spite of the inadequate treatment, and we submit that they did not have syphilis at all. The entire group has been included in the non-syphilitic classification, although if they should be discarded from the series, it would not change the results appreciably.

Of the four infants followed for less than a year, two were transferred for treatment to private physicians as soon as the Wassermann tests were found to be positive for syphilis, and they were not followed. The other two were treated, and both died, one at three weeks and the other at seven weeks, of hemorrhagic encephalitis as a result of sulpharsphenamine injections given for syphilitic infections they probably never had.

In the mothers, the diagnosis of syphilis was made on the basis of history, physical findings and blood tests. When it was necessary to make a diagnosis on blood tests alone, the tests were always repeated at least once if the first was strongly positive and several times over a period of several weeks if doubtfully positive. We have never felt that the requirements for a definite diagnosis of syphilis should be altered because of pregnancy or that treatment should be started until a reasonably certain diagnosis had been made. After this study we are more than ever convinced of the propriety of this viewpoint.

The status of the infant according to the time when the mother was treated is shown in Table 1.

TABLE 1.—*Outcome of Treatment According to Time of Treatment of Mother*

Treatment	Outcome	
	Syphilitic	Non-syphilitic
None	5	17
During pregnancy	5	96
Before pregnancy	0	98
Before and during pregnancy	0	120

It should be noted that none of the ten syphilitic infants were born of mothers who had received treatment prior to pregnancy.

The outcome in all women who received no antisyphilitic therapy before the start of pregnancy is summarized in Table 2, according to the number of injections of trivalent arsenic that were given during pregnancy. In nearly every case a corresponding number of injections of bismuth was given in addition. Bismuth alone and penicillin were given to a few patients as noted.

TABLE 2.—*Outcome of Pregnancy According to the Amount of Treatment Given During Pregnancy to Patients Who Had Had None Before*

Treatment	Outcome	
	Syphilitic	Non-syphilitic
None	5	17
Bismuth only	1	3
Injections of arsenic:		
1 - 4	1	14
5 - 9	2	31
10 - 14	1	19
15 or over	0	17
Penicillin	0	12
Total	10	113

From Table 2 it is evident that only a moderate amount of therapy is required to prevent the transmission of syphilis to the infant, since in only one instance was the child infected when the mother was given more than ten injections of arsenic.

All the pregnancies not included in Table 2 were preceded by antisyphilitic therapy. The amount of this treatment together with the outcome is shown in Table 3. Some of these mothers received additional treatment during pregnancy but this had no apparent effect upon the results of the previous therapy.

TABLE 3.—*Outcome of Pregnancy According to the Amount of Treatment Given Before Pregnancy*

Treatment	Outcome	
	Syphilitic	Non-syphilitic
Bismuth only	0	2
Injections of arsenic:		
1 - 9	0	33
10 - 19	0	50
20 - 29	0	45
30 - 39	0	36
40 or over	0	43
Penicillin	0	9
Total	0	218

Although most of these women had received considerable amounts of therapy, it is evident that even small amounts afford a considerable degree of protection if given prior to conception, since 35 pregnancies were preceded by fewer than ten doses of arsenic and an additional 50 had fewer than the standard 20 doses without a single syphilitic baby as a result.

In addition to the amount of treatment administered to the syphilitic mother, there are two other important factors to be taken into consideration. These are the stage of pregnancy in which treatment is started and the duration of the infection in the mother. In all five cases in which a syphilitic child was born after treatment, the infection in the mother was not discovered until the last trimester when the fetus is already infected and treatment necessarily less effective.

The effect of the duration of the infection on the outcome is difficult to determine because of the uncertainty that exists as to the onset of syphilis in most women. In 154 of the cases in this series, there was no clue to the duration whatever. In 96 it was

known to be in excess of four years but the date of onset was frequently lacking, and in 59 it was of less than 4 years' duration. Thirty-two mothers had congenital syphilis. Among the infants who had syphilis, delivery occurred when the infection in the mother was early in five and when the time of infection was unknown, but probably recent, in four. In one case the mother had quite definite stigmata of prenatal syphilis, in spite of which, tests of the child's blood showed positive reactions, with a rising titer and a positive darkfield from the nasal secretions. This mother was untreated and this was the only case observed in which the infection in a late stage in the mother was transmitted to the child.

In 59 pregnancies, the infection in the mother at the time of delivery was known to be early, that is, of less than four years' duration. Although the number is small, the outcome of pregnancy in relation to treatment is of interest and is summarized in Table 4.

TABLE 4.—*Outcome of Pregnancy in Patients With Early Syphilis at the Time of Delivery According to the Time and Amount of Treatment*

Treatment	Outcome	
	Syphilitic	Non-syphilitic
None	2	3
During pregnancy:		
Arsenic, 1 - 9 doses	2	10
10 or more doses	1	11
Penicillin	0	11
Before pregnancy:		
Arsenic, 10 - 19 doses	0	6
20 or more doses	0	6
Penicillin	0	7
Total	5	54

Even with very little treatment, it is not unusual for a woman with early syphilis to give birth to a normal child. This occurred in 13 of 17 patients who were given fewer than ten injections of arsenic during pregnancy. More than this amount of therapy gave almost complete protection against congenital transmission, the single failure in the higher treatment group having been in the case of a mother who had had just ten doses of mapharsen and five of bismuth. The principal period of danger to the infant is certainly when the mother has early syphilis at delivery, but even then transmission is not a certainty, and it may be prevented by relatively small amounts of treatment.

Penicillin given either before or during pregnancy never failed to protect the child from syphilis. In several cases it was given in the last month of pregnancy and in several the total dose was only 300,000 units. This result is in complete agreement with the findings of other observers (Ingraham[5]).

The status of the mother's blood at the time of delivery with regard to reactions to tests for syphilis, is often cited as a factor in determining the transmission of syphilis to the infant. To a limited extent this is true in that a woman who is seronegative at delivery seldom has a syphilitic child. On the other hand it is common for a seropositive woman also to have a normal child. In the ten pregnancies in our series that resulted in syphilitic infants, the reaction of the mother's blood to tests for syphilis was known in nine cases: It was positive in eight and doubtful in one. The comparative results of tests of the mother's blood and of blood from the cord in all pregnancies in which the reaction of the mother's blood was known are given in Table 5. The tests of the mother's blood were not always done at exactly the time of delivery, but were never more than two months away.

TABLE 5.—*Results of Tests on Cord Blood in Relation to Mother's Blood at Approximate Time of Delivery*

Mother's Blood	Number	Cord Blood	
		Positive	Negative
Positive	163	65 (40%)	98 (60%)
Negative	150	21 (14%)	129 (86%)

It will be seen that the infant's blood is much more likely to show positive reaction if the mother's does. However, there is no complete agreement between them, and the diagnosis in the child should be made without regard to the status of the mother.

DISCUSSION

In an inquiry into the effect of syphilis in the mother upon the offspring, the most important single consideration is the accuracy of diagnosis in the child. It has been customary to assume that every abortion or stillbirth that terminates a pregnancy in a patient with syphilis is due to the infection. This is a grossly misleading custom and should be abandoned. If an autopsy shows syphilis in the fetus, the termination may be ascribed to syphilis. If no evidence of the disease is found on careful examination, the infection should not be blamed. If the fetus has not been examined, the case should be excluded from consideration.

When an infant is born alive to a mother with syphilis, a diagnosis of syphilis is justified in the child only when there develops some clinical evidence of syphilis or when serial tests of the blood by a quantitative method show a rising reagin titer. The persistence of a positive qualitative reaction for an arbitrary period of time such as one or two months does not justify a diagnosis of syphilis.

On the basis of our experience, we believe that the danger of transmitting syphilis from mother to child during pregnancy is less than it has generally been considered to be. Only 10 of 341 infants were proved to have syphilis, and these were born of mothers who had had no treatment, or very little, and in all but one of whom the infection at the time of delivery was either definitely or probably early.

In no case in which the mother had received antisyphilitic therapy prior to conception was the infection transmitted to the child. This and similar observations by other observers[7] lead us to disagree sharply with the dictum of the Cooperative Clinical Group (Cole and his co-workers[1]), that "The safer procedure then for every mother who has or ever has had syphilis is to take antisyphilitic treatment throughout each pregnancy."

This policy is absolutely unjustified, since it adds a definite risk and considerable inconvenience and discomfort to pregnancy without demonstrable benefit. Since penicillin is harmless and very effective, one might be justified in using it in these circumstances but it should not be insisted upon if the mother has had a reasonable amount of previous treatment.

When the infection in the mother is early or when she has been untreated before pregnancy, antisyphilitic therapy should always be given, starting as early as possible after gestation, but never unless a definite diagnosis of syphilis can be established. Much more harm can be done by giving treatment on suspicion, thereby permanently preventing proper diagnosis, than is likely to occur if a patient in whom the existence of the disease is questionable is left untreated. Since penicillin is both safe and effective in early congenital infections, a great deal of the hazard of prental syphilis is now removed and one is entitled to take somewhat greater chances with the outcome in the infant to the benefit of the mother than was justified before penicillin was available.

SUMMARY

1. The outcome of 341 pregnancies in 243 mothers with syphilis is reported, according to the time and amount of treatment that the mother received.

2. Only ten infants were found to be infected, none as a result of a pregnancy that had been preceded by treatment.

3. The diagnosis of syphilis in mother and child is discussed together with some factors that affect the outcome.

4. It is concluded that the hazards of syphilis in pregnancy are not as great as they are usually considered to be if the diagnosis of syphilis in the infant is carefully made.

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Discussion by A. FLETCHER HALL, M.D.

I am sure that we all welcome this timely blast from one of syphilology's outstanding iconoclasts. As a matter of fact he is not the first to cite cases in support of the stand which he has taken, although he is the first, so far as I know, to advocate such radical conclusions.

As early as 1927 Birnbaum reported that 21 women presumably cured of syphilis gave birth to 34 normal infants but no syphilitics; in 1934, Cole, reporting the material of the Clinical Cooperative Group, added 54 adequately treated syphilitic women who gave birth to no syphilitic children in pregnancies subsequent to their treatment; in the same year, McKelvey and Turner, reporting on the material at Johns Hopkins Hospital, stated that 59 syphilitic women receiving a minimum of 1 gm. of arsphenamine (three or four treatments) before pregnancy, gave birth to only healthy infants, while those who received no treatment before pregnancy required four to five times as much during pregnancy to prevent the appearance of syphilis in their offspring. These findings parallel those reported to us in Dr. Barnett's paper. Findlay in 1942, commenting on his experience with syphilitic women adequately treated before pregnancy, stated, "It is difficult to understand how most writers recommend that further courses of salvarsan therapy should be carried out through any succeeding pregnancy."

Although all of the preceding quotations are taken from Stokes, "Modern Clinical Syphilology," Third Edition (1944), that author states as his opinion in the same text, "Conservative opinion suggests that with our present-day knowledge, a syphilitic woman should be treated through every pregnancy, regardless of the duration of her infection, her serologic status, or the amount or type of antecedent therapy." Moore (in 1943: "The Modern Treatment of Syphilis," Second Edition) quotes McKelvey and Turner's and the Cooperative Clinical Groups' figures as listed above, and agrees with the former that thorough treatment of the maternal syphilis *prior* to pregnancy, i.e., not less than four gm. of arsphenamine with appropriate heavy metal, probably affords adequate protection of the offspring in subsequent pregnancies even though treatment during the pregnancy is omitted." He further states that, "They feel, however, that if the maternal serologic test remains positive, or if there is clinical evidence of persistent infection, it seems wise to treat the mothers during pregnancy, regardless of the amount of previous treatment." Moore does not comment on this last quotation.

Stokes and Moore are undoubtedly the most referred to authorities on the conduct of the treatment of syphilis, and rightly so because there is certainly no more comprehensive and dependable compendium of information in this field than either of these texts represents. It is to be hoped that future editions will carry the material presented in Dr. Barnett's present paper, giving appropriate weight to his conclusions.

It is only by giving such weight to the findings reported in this excellent paper, and those previously reported, that we who treat syphilis, whether we be "specialists" or general practitioners, will dare to stop subjecting pregnant syphilitic women to unnecessary and dangerous treatment, just as a sop to our own perhaps too zealously guarded peace of mind.